Gestational diabetes mellitus (GDM) is defined as insulin resistance of variable severity with onset or first recognition during pregnancy. The prevalence of GDM in the US is growing with approximately 7% of pregnant women now being diagnosed.(ACOG, 2011) The rising prevalence of GDM is associated with the increasing rates of overweight and obesity. Maternal adverse outcomes associated with GDM include preeclampsia, cesarean delivery, and an increased risk of developing type-2 diabetes later in life.(ACOG, 2001) Risks for the fetus and newborn include macrosomia, birth trauma, hyperbilirubinemia, hypoglycemia, respiratory distress syndrome, and childhood obesity.(ACOG, 2001) Appropriate diagnosis and treatment of women with GDM reduces fetal macrosomia, preeclampsia, gestational hypertension, cesarean delivery, and composite neonatal morbidity (shoulder dystocia, nerve palsy, and bone fracture). (M. B. Landon et al., 2009) **APEC recommends that <u>all</u> women, except those overtly diabetic, be screened for gestational diabetes mellitus.**

<u>Screening & Diagnostic Tests Available</u>

As noted in the Hyperglcyemia and Adverse Pregnancy Outcomes study, the relationship between hyperglycemia and adverse pregnancy outcomes is continuous, i.e. there is no distinct cut-off between "normal" and "abnormal" blood sugars associated with "good" and "bad" pregnancy outcomes. (HAPO, 2008) The result is that there continues to be much debate about the screening and diagnostic criteria used to diagnose GDM.

Two-Step Approach

- Non-fasting 1-hour, 50-g load with cutoff between 130-140 mg/dL. If one hour exceeds cutoff, proceed with fasting, 100-g 3 hour test. Diagnosis requires 2 abnormal values on 3-hour testing (NOTE: if FBS is > 126 mg/dL, do not proceed with glucose solution)
- Recommended/endorsed by ACOG
- Does not require fasting for first step
- Prevalence of GDM with this test ~5%
- Long-standing use in obstetric practice

One-Step Approach

- Fasting 75-g glucose load with diagnosis after 1 abnormal value.
- Recommended/endorsed by IADPSG
- All patients must be fasting
- Prevalence of GDM with this test 15-40%

Currently, two recommendations exist for the screening and diagnosis of GDM, a two-step and a one-step approach. The two-step approach consists of a 1-hour, 50-g glucose challenge followed by a 3-hour, 100-g glucose tolerance test. The one-step approach consists of a 2-hour, 75-g glucose tolerance test. Each test has advantages and disadvantages (see box). APEC recommends the two-step approach given the abundance of data on its

use in pregnancy. This method was recently endorsed at the NIH Consensus Development Conference on Diagnosing Gestational Diabetes Mellitus. (NIH, 2013)

50-gram Screening

All pregnant women should be screened for GDM at 24-28 weeks GA with a 50-gram oral glucose 1-hr loading test.(ACOG, 2001, 2011) In women at high risk for GDM based on a prior history of GDM, marked obesity, a family history of type-2 DM, or women with repetitive glycosuria, consideration should be given to early testing between 12-20 weeks GA.(ACOG, 2001) If the patient tests positive for GDM at ≤20 weeks, it is likely that glucose intolerance preceded pregnancy and she should be treated as a type-2 diabetic. If the early screen is negative, these women should be re-screened at 24-28 weeks.

Indications for Consideration of Early GDM Screening (12-20 weeks)
GDM in prior pregnancy
Type 2 DM in first degree relative (e.g. parent, sibling)
Obesity
Repetitive glycosuria

A 50-gram oral glucose load can be administered without regard to time of last meal or time of day. A venous plasma level is measured at 1 hour after the glucose load. During fasting, capillary and venous blood have similar glucose concentrations, but after a meal or glucose challenge, capillary glucose is higher than venous glucose; thus, capillary blood (i.e. fingersticks) should **not** be used for the screening or diagnosis of GDM.(ACOG, 2001) Cutoff thresholds ranging from 130-140 mg/dL have been proposed with no one cutoff accepted universally. In an attempt to balance detection with the number of women requiring a 3-hr test, APEC recommends using **135 mg/dL** as the threshold for diagnostic testing. Using a cut-off of 135, the sensitivity for GDM is between 80-90% with a false positive rate of 10-15%. Between 15-25% of patients will require a diagnostic glucose tolerance test using this criterion.

Since the 50-g load is a screening test, abnormal screening tests should be followed by a diagnostic, 100-g glucose load. Although the value of the 50-g load is predictive of the 100-g test results, no absolute value for the 50-g load exists above which all patients will be diagnosed with GDM. For example, the positive predictive value of a 1-hour of 200 is roughly 50%. Therefore, a significant number of patients will be spared a diagnosis of GDM by following even high 1-hour glucose challenge tests with a 100-g glucose tolerance test. There is a concern that a 100-g glucose load could precipitate marked hyperglycemia in pregnant women, therefore a fasting blood sugar should be performed prior

to administering the glucose solution. A fasting blood sugar ≥126 mg/dL is diagnostic of diabetes and the solution does not have to be administered.

For the 100-gram OGTT, the patient should fast overnight with a venous plasma level drawn first. If the fasting venous plasma level is ≥ 126mg/dL, the glucose load is not administered and the patient is diagnosed with GDM. If the value is < 126mg/dL, the patient should consume the 100-gram glucose load and have venous plasma levels at 1, 2, and 3 hours. Two or more of the four values above the 4th International Workshop Criteria (aka Carpenter & Coustan Criteria(Carpenter, 1982)) establish the diagnosis of GDM.

Table 1 Venous plasma concentrations for positive diagnosis of diabetes mellitus

Status	4th International Workshop Criteria (mg/dL)
Fasting	95
1 hour	180
2 hour	155
3 hour	140

*At Least 2 abnormal values required for diagnosis

Alternative GDM screening

Some women cannot tolerate the hyper-osmolar glucose solution used for GDM screening, as it can cause gastric irritation, delayed emptying, and gastrointestinal osmotic imbalance. The glucose load may precipitate dumping syndrome in patients with a history of gastric bypass and should therefore not be performed in these women. In patients with a history of bariatric surgery and other patients who are unable to tolerate the OGTT, alternative screening consists of fasting and 1- or 2-hour postprandial capillary blood glucose measurements collected for one week. Ideal blood glucoses are FBS <95 mg/dL, 1-hour postprandial <140 mg/dL, and 2-hour postprandial <120 mg/dL. If blood glucoses are in the normal range for one week, no further testing is necessary. If >50% of blood glucose determinations are abnormal, the patient should be treated as a gestational diabetic. If 25-50% of blood glucose determinations are abnormal, the patient should be given dietary counseling and repeat another week of blood sugars after dietary modifications. For patient in whom alternative screening is utilized, it should be done at 24-28 weeks as routine and 12-20 weeks for women at high risk for GDM.

White's Classification of GDM:

1. A1: abnormal OGTT, controlled with diet
2. A2: abnormal OGTT, requires medication for glycemic control (oral agent or insulin)

Pregnancy Management

Diet modification, exercise, and frequent blood sugar assessments, with hypoglycemic agents if needed, are the key management tools for glucose control. Patients should be encouraged to keep a log of food intake correlated with exercise, glucose values, and doses of hypoglycemic agent(s), if applicable.

Diet modification

All GDM patients require nutritional counseling with a registered dietician or diabetic educator. Nutritional intervention in women with GDM should be designed to achieve normal glucose levels and avoid ketosis, while maintaining appropriate nutrition and weight gain.(ACOG, 2001) Daily caloric recommendations are based on the patient's pre-pregnancy weight with 35-40 kcal/kg for the underweight patient, 30-35 kcal/kg for the normal weight patient and 25 kcal/kg for the overweight patient. The diet should consist of 40-50% complex carbohydrates, 20-30% fat, and 20-30% protein. Concentrated sweets should be excluded. Total weight gain recommendations for pregnancy are BMI-specific and are not altered by diabetes.

Exercise

All women should follow a program of moderate exercise (30 minutes of walking at least 5 times per week) as part of the treatment plan, barring any medical or obstetrical contraindication to this level of physical activity.

Blood Glucose Monitoring

Women should be advised to monitor their blood sugars at least 4 times/day: fasting (AM) and postprandial (breakfast, lunch, dinner). Postprandial blood sugars may be monitored 1- or 2-hours after a meal and may be individualized for patient ease and convenience. Ideal blood sugars are FBS <95 mg/dL, 1-hour

Table 2. Self-monitored Capillary Blood Glucose Goals

Specimen	Level (mg/dL)
Fasting	< 95
Premeal	< 100
1-hr postprandial	< 140
2-hr postprandial	< 120
0200-0600	> 60
Mean (average)	100
Hb A1c	≤ 6%

postprandial <140 mg/dL, and 2-hour postprandial <120 mg/dL(Mark B. Landon & Gabbe, 2010). Blood sugars should be reviewed by the healthcare provider after one (1) week.

- If more than half (50%) of the blood sugars are within the ideal range, the patient may reduce blood sugar checks to four (4) determinations one day per week (usually done on the day prior to returning to her clinic visit).
- If more than half (50%) of the blood sugars are above the ideal range (fasting levels >95 mg/dL, 1-hour postprandial values >140 mg/dL, 2-hour postprandial values >120 mg/dL) despite compliance with diet, the patient will require medical management with glyburide or insulin and is now classified as an A2 gestational diabetic. A2 patients require daily blood sugar monitoring for the rest of their pregnancy.

Oral Hypoglycemic agents

In a large randomized trial by Langer et al., oral glyburide was demonstrated to achieve perinatal outcomes similar to those achieved with insulin therapy in pregnant women.(Langer, Conway, Berkus, Xenakis, & Gonzales, 2000) Given the ease of oral versus insulin treatment, this agent is considered an acceptable treatment alternative for GDM. Glyburide is a second generation sulfonylurea, which works by stimulating the pancreas to release more insulin. Its onset of action is 4 hours and it lasts for approximately 10 hours. The recommended starting dose is 2.5mg twice a day, which can be increased at 2.5mg increments for a maximum dose of 10mg twice daily. For patients who fail to achieve glycemic goals of FBS <95mg/dL, 1-hour postprandial <140mg/dL, and 2-hour postprandial <120mg/dL, doses should be escalated at least weekly up to the maximum. If >50% of the blood sugars are suboptimal despite the maximum dose of glyburide and diet compliance, the patient should be switched to insulin therapy.

Insulin

The goal of insulin therapy is to mimic the physiology of the pancreas: a basal rate of insulin release to allow glucose uptake into cells, a bolus of insulin with meals to inhibit gluconeogenesis and lipolysis and avoid hyperglycemia. Patients requiring insulin therapy will need additional diabetic education on the use of insulin and hypoglycemia management with a registered dietician or diabetic educator. Hospitalization is not necessary but may be useful in select patients to initiate insulin therapy. The starting insulin dose is calculated based on the patient's weight. APEC recommends the use of a

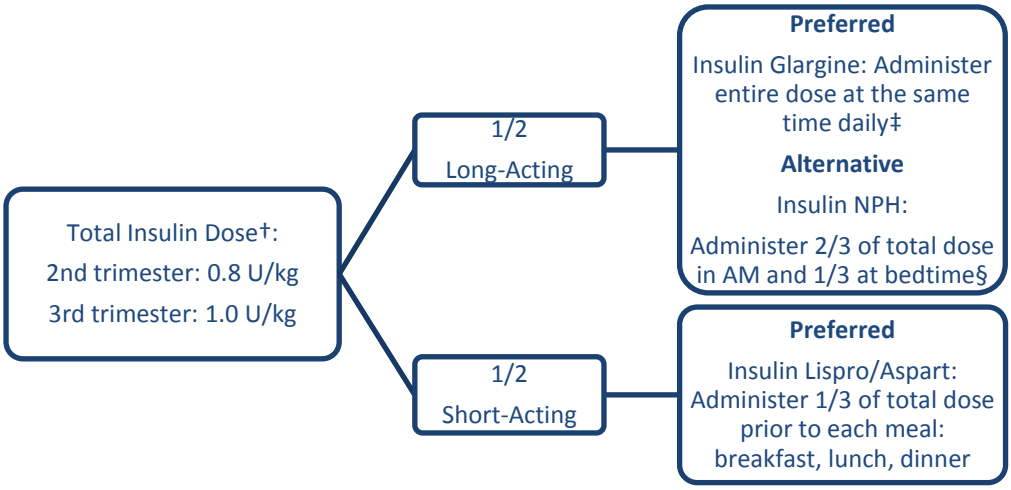
basal-bolus approach using insulin glargine with rapid-acting insulin at each meal. This is based on evidence that this regimen provides excellent glycemic control, maximum patient flexibility and satisfaction, and minimizes hypoglycemic episodes.

Table 3. Action profile of commonly used insulin (Gabbe & Graves, 2003)

Insulin	Onset of action	Peak of action (hrs)	Duration (hrs)
Lispro/Aspart (Humalog, Novolog)	Rapid-1-15 min	1-2	4-5
Regular	Short 30-60 min	2-4	6-8
Neutral Protamine Hagedorn (NPH)	Intermediate 1-3 hrs	5-7	13-18
Glargine (Lantus)	60	Mild at 6-8	24
rDNA insulin detemir (Levemir)	120-240	Mild at 3-9	dose dependent

*Levemir dose of 0.2 U/kg last 5-12 hrs, 0.4 U/kg last 19 hrs, 0.8 U/kg last 24 hrs. Levemir may be dosed once or twice a day.

All patients on insulin should receive education on insulin use, signs and symptoms of hypoglycemia, and a prescription for a glucagon kit. Below is the formula for starting a patient on a weight-based insulin regimen. Some women with GDM may respond to a single injection of insulin glargine. The weight-based dose as calculated below may be started without starting short-acting insulin and blood sugars monitored for one week to determine whether pre-meal insulin is needed. However, women with severely elevated postprandial blood sugars, or markedly abnormal 3-hr GTT results, will likely require pre-meal rapid-acting insulin.



† For insulin naïve subjects, consideration may be given to reducing the starting dose by 25% with aggressive titration up after 3-7 days of blood glucose monitoring.
‡ The maximum dose of insulin glargine that should be administered in one injection is 70 units. If a patient requires more than 70 units of insulin glargine, administer as BID dosing.
§ The evening dose of NPH may be administered at dinner to reduce the number of injections; however this strategy is associated with an increased frequency of night-time hypoglycemia.

Adjustments to Insulin Therapy

- Adjustments to long-acting insulin glargine should not be made more frequently than every 48 hours.
- Adjustments to insulin regimen should be made when >50% of blood sugars are greater than target (FBS >95 mg/dL, 1-hour postprandial >140mg/dL, 2-hour postprandial >120mg/dL).
- Adjustments to long-acting insulin will correct fasting blood sugars.
- Adjustments to pre-meal short acting insulin will correct the postprandial blood sugar for that meal.
- Increases to insulin can be made in increments of 10%. For patients in the inpatient setting, more aggressive dose-adjustment can be performed in the face of marked hyperglycemia.

Safety & Counseling

- Fast-acting insulin should not be injected unless the patient is planning to eat immediately.
- Any patient on insulin should receive a prescription for a glucagon kit. At least one family member or housemate should be instructed on how and when to administer glucagon.

Medical Management

A1 GDM

- Diet-controlled GDM does not place the pregnancy at increased risk of stillbirth.
- Blood glucose monitoring: one day per week to monitor for worsening glycemic status and need for hypoglycemic medications.
- Weekly antenatal testing starting at 40 weeks gestation.
- Ultrasound for growth within 3 weeks of delivery (typically at 36-37 weeks) to evaluate for macrosomia.
- If estimated fetal weight exceeds 4200-4500 grams, cesarean delivery should be offered.
- Delivery by 41 weeks gestation.

A2 GDM

- GDM requiring hypoglycemic agents does place the pregnancy at an increased risk of stillbirth.
- Blood glucose monitoring: 4 times daily for the remainder of pregnancy.
- Patients should be seen weekly until medications are titrated to achieve adequate control.
- Prior to 32 weeks, once adequate blood sugar control is attained, visits can occur every 2 weeks. After 32 weeks, visits should occur weekly.
- Weekly antenatal testing starting at 32 weeks. Patients with poor glycemic control, as evidenced by blood sugar logs, EFW >90th percentile, or polyhydramnios, may require twice weekly testing.
- Ultrasound for growth within 3 weeks of delivery (typically at 36-37 weeks) to monitor for macrosomia.
- If estimated fetal weight exceeds 4200-4500 grams, cesarean delivery should be offered.
- Delivery between 39-40 weeks gestation.

Delivery and Postpartum Management

The goal of intrapartum management is a blood sugar at the time of delivery <120 mg/dL in order to minimize the risk of neonatal hypoglycemia after cord clamping. Diabetics should not be denied glucose in order to achieve this goal; rather, they should be managed with D5 and insulin

infusion as necessary. It is exceedingly rare that an A1 would need any treatment intrapartum and most A2 will not. However, if a patient develops ketonuria and D5 or D10 infusions are initiated, the blood sugars should be followed and any elevations (>120 mg/dL) treated with insulin. Small doses of rapid-acting insulin can be administered subcutaneously rather than initiating a continuous infusion for only mild elevations. If repetitive dosing is required, consideration should be given to a continuous insulin infusion.

Patients with GDM are cured by delivery; all medications can be stopped post-partum. However, some patients with GDM have undiagnosed Type 2 diabetes. Therefore, a single post-partum fasting blood sugar can be used to screen patients for undiagnosed Type 2 diabetes prior to discharge. If ≥126 mg/dL, continue monitoring patterned blood sugars and treat as needed.

Approximately 15-20% of patients will have continued glucose intolerance or frank diabetes at 6 weeks post-partum. Patients with GDM should be screened for Type 2 DM at 6-8 weeks after delivery with a 75-gram, 2 hour glucose tolerance test. (ACOG, 2009) This testing should be scheduled when the patient returns for her post-partum exam or the patient should be instructed to follow-up with her primary care physician. For women who are exclusively breastfeeding, it is reasonable to wait until they are done lactating prior to performing screening. Women with gestational diabetes require life-long monitoring for Type 2 diabetes and should be instructed on the importance of continued care with their primary care physician.

	Fasting (mg/dL)	**2 hour (mg/dL)**
Normal	<110	<140
Impaired Glucose Tolerance	110-125	140-199
Diabetes	≥126	≥200

Quality Indicators/Benchmarks

- GDM screening-all patients except overt diabetics
- Diabetic education before 32 weeks for diagnosed GDM

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